# Letters

RESEARCH LETTER

## Association Between Gadolinium Contrast Exposure and the Risk of Parkinsonism

Gadolinium-based contrast agents are used for enhancement during magnetic resonance imaging (MRI). Safety concerns have emerged over retained gadolinium in the globus pallidi.[1,2] Neurotoxic effects have been seen in animals and when gadolinium is given intrathecally in humans.[1] In July 2015, the US Food and Drug Administration stated that it was unknown whether gadolinium deposits were harmful. The substantia nigra (affected in Parkinson disease) directs voluntary movement via signals to the globus pallidi. Consequences of damage to the globus pallidi may include parkinsonian symptoms.[3] We conducted a population-based study to assess the association between gadolinium exposure and parkinsonism.

Supplemental content at jama.com

**Methods** | Sunnybrook Hospital granted ethics approval and deemed the study exempt from participant consent. Multiple linked administrative databases from Ontario, Canada, were used. The population has universal health care, and medication coverage is provided for those older than 65 years. Using fee codes submitted by radiologists, all patients older than 66 years who underwent an initial MRI between April 2003 and March 2013 were identified. Patients whose

Table 1. Selected Baseline Characteristics for Patients With vs Without Gadolinium Exposure[a]

| | Exposure, No. (%) | | |
|---|---|---|---|
| | Only Non-Gadolinium-Enhanced MRIs[b] (n = 146 818) | ≥1 Gadolinium-Enhanced MRI[c] (n = 99 739) | Standardized Difference[d] |
| Demographics | | | |
| Age, median (IQR), y | 72 (68-77) | 73 (69-78) | 12 |
| Women | 81 795 (55.7) | 53 647 (53.8) | 4 |
| Rural residence | 19 972 (13.6) | 11 409 (11.4) | 7 |
| Socioeconomic status | | | |
| Lowest quintile | 24 296 (16.5) | 17 660 (17.7) | 3 |
| Highest quintile | 34 646 (23.6) | 22 696 (22.8) | 2 |
| Comorbidities in the past 5 y | | | |
| Dementia | 8262 (5.6) | 6272 (6.3) | 3 |
| Stroke | 2644 (1.8) | 3296 (3.3) | 10 |
| Cancer (bowel, breast, prostate, lung, rectal) | 18 890 (12.9) | 27 705 (27.8) | 38 |
| Melanoma | 2076 (1.4) | 1803 (1.8) | 3 |
| Seizure | 403 (0.3) | 419 (0.4) | 2 |
| Encephalitis, multiple system atrophy, progressive supranuclear palsy, primary lateral sclerosis | 21 (<0.1) | 9 (<0.1) | 0 |
| Comorbidity score, median (IQR)[e] | 9 (6-11) | 9 (7-12) | 17 |
| Medication use in the past 6 mo | | | |
| Atypical antipsychotics | 2044 (1.4) | 1515 (1.5) | 1 |
| Other antipsychotics | 1135 (0.8) | 2050 (2.1) | 11 |
| Antidepressants | 13 041 (8.9) | 8190 (8.2) | 3 |
| Cholinesterase inhibitors | 1894 (1.3) | 1358 (1.4) | 1 |
| SSRIs | 11 375 (7.7) | 7720 (7.7) | 0 |
| Anticholinergics | 4262 (2.9) | 2809 (2.8) | 1 |
| Healthcare utilization in the past year | | | |
| No. of prior neurology visits | | | |
| 0 | 133 229 (90.7) | 86 611 (86.8) | |
| ≥1 | 13 589 (9.3) | 13 128 (13.2) | 6 |
| No. of prior hospitalizations | | | |
| 0 | 99 911 (68.1) | 52 853 (53.0) | |
| ≥1 | 46 907 (31.9) | 46 886 (47.0) | 14 |
| Prior computed tomography of the head | 16 903 (11.5) | 18 391 (18.4) | 19 |

Abbreviations: ADG, Aggregated Diagnostic Group; IQR, interquartile range; MRI, magnetic resonance imaging; OHIP, Ontario Health Insurance Plan; SSRIs, selective serotonin reuptake inhibitors.

[a] Patients were dichotomized into those with and without gadolinium exposure, and baselines were determined relative to the date of the initial MRI. A full list of measured covariates is included in the Supplement.

[b] MRI patients were identified using OHIP fee codes X431 and X435 (neck); X441 and X445 (thorax); X451 and X455 (abdomen); X446 and X447 (breast); X461 and X465 (pelvis); and X471, X475, X488, and X489 (extremity).

[c] Administration of gadolinium during an MRI was identified using the OHIP code X487, and patients could switch from those with no gadolinium exposure to those exposed to gadolinium at any time during follow-up. The total number of gadolinium-enhanced MRIs in this cohort was 129 120.

[d] Standardized differences were calculated using the group mean difference divided by the pooled SD, and they identify potential clinically significant differences (>10%) between large groups in population-based studies independent of the large sample size.

[e] Measured by the Johns Hopkins ADG system, which assigns a score to patients based on their health care utilization and the severity and chronicity of the medical problems for which they access health care services.

Table 2. New Diagnoses of Parkinsonism After MRIs (Not of the Brain or Spine) With or Without Gadolinium Exposure

| Primary Analysis | Entire Cohort (N = 246 557) | Exposed to Only Non-Gadolinium-Enhanced MRIs (n = 146 818) | Exposed to Gadolinium-Enhanced MRIs | | HR (95% CI) | *P* Value |
|---|---|---|---|---|---|---|
| | | | ≥1 MRI (n = 99 739) | ≥4 MRIs[a] (n = 2446) | | |
| Total follow-up, person-years | 991 937 | 625 185 | 366 752 | 6634 | | |
| Primary outcome, No. (%) | 2861 (1.16) | 1697 (1.16) | 1164 (1.17) | 17 (0.70) | | |
| Rate (95% CI)[b] | 2.88 (2.78-2.99) | 2.71 (2.59-2.84) | 3.17 (2.99-3.36) | 2.56 (1.54-4.02) | | |
| Unadjusted analysis[c] | | Reference | | | 1.08 (1.04-1.13) | <.001 |
| Adjusted analysis[d] | | Reference | | | 1.04 (0.98-1.09) | .18 |
| Sensitivity analysis | | | | | | |
| Post hoc analysis 1[e] | | Reference | | | 0.99 (0.94-1.03) | .58 |
| Post hoc analysis 2[f] | | Reference | | | 1.03 (0.98-1.09) | .29 |

Abbreviations: HR, hazard ratio; MRI, magnetic resonance imaging; SSRIs, selective serotonin reuptake inhibitors.

[a] Patients exposed to 4 or more MRIs with gadolinium are a subset of those who are exposed to 1 or more MRIs with gadolinium.

[b] Per 1000 person-years of observation.

[c] HR per additional gadolinium exposure.

[d] Adjusted analysis used the same statistical model and included 38 covariates selected from the 105 measured covariates that were either potential confounders or unbalanced at baseline (standardized difference, >10%). Specific covariates included demographics (age, sex, year of cohort entry, MRI study body part), comorbid conditions (dementia, stroke, solid organ cancer [bowel, lung, breast, prostate, rectal], melanoma, seizure, comorbidity score, congestive heart failure, coronary artery disease, hypertension, chronic liver disease, chronic kidney disease), medications (antipsychotics, atypical antipsychotics, antidepressants, cholinesterase inhibitors, SSRIs, anticholinergics, androgen deprivation therapy, antiplatelets, β-blockers, calcium-channel blockers, angiotensin-converting enzyme inhibitors, corticosteroids, total number of unique drug names), and health care utilization (number of hospitalizations, number of neurology visits, computed tomography of the head, echocardiogram, Holter monitor, carotid ultrasound).

[e] Post hoc analysis 1 had further adjustment for 12 additional covariates with standardized differences of 9% or 10%: atrial fibrillation or flutter, peripheral vascular disease, antineoplastic agents, narcotics, non–potassium-sparing diuretics, number of family physician visits, bone scan, cardiac catheterization, cardiac stress test, prior spine MRI, prior urine culture, prior chest x-ray.

[f] Post hoc analysis 2 was an adjusted analysis using an outcome definition independent of parkinsonism medications.[4]

initial MRI was of the brain or spinal cord and those with prior parkinsonism or neurosurgery were excluded. Patients who were exposed to gadolinium-enhanced MRIs (modeled as a time-varying, cumulative count variable) were compared with patients who received non-gadolinium-enhanced MRIs. The primary outcome, assessed from the initial MRI until death, emigration, or March 2015, was a new diagnosis of parkinsonism based on a validated definition (sensitivity, 81.7%; specificity, 99.7%; positive predictive value, 78.0%; negative predictive value, 99.8%; accuracy, 99.5%; and disease prevalence, 1.4%) using diagnosis codes from hospital admissions and physician visits or a dispensed Parkinson disease–specific medication.[4] We measured 105 covariates[5] and evaluated significant inequalities between patients who underwent only non-gadolinium-enhanced MRIs and those who underwent 1 or more gadolinium-enhanced MRI. A subset of 38 covariates particularly relevant to parkinsonism (based on potential associations from the literature) or significantly different at baseline (standardized difference >10%) were included in a multivariable time-dependent extended Cox regression model using SAS (SAS Institute), version 9.4; the hazard ratio (HR) is interpreted as the hazard of parkinsonism per additional gadolinium exposure.[6] Sensitivity analyses adjusting for covariates with standardized differences of 9% or 10% and defining parkinsonism without medications[4] were performed. A 2-sided *P* value less than .05 was considered significant.

**Results** | Of the 246 557 patients (median age, 73 years [interquartile range, 69-78]; women, 54.9%) undergoing at least 1 MRI (not of the brain or spine) during the study period, 99 739 (40.5%) received at least 1 dose of gadolinium. The most common initial non-gadolinium-enhanced MRI was of an extremity (76.0%); the most common gadolinium-enhanced MRI was of the abdomen (39.2%). Among patients who underwent gadolinium-enhanced MRIs, 81.5% underwent a single study, and 2.5% underwent 4 or more gadolinium-enhanced studies. Incident parkinsonism developed in 1.16% of unexposed patients and 1.17% of those exposed to gadolinium. Selected covariates are summarized in **Table 1** (and listed in eTable 1 in the Supplement). In adjusted analysis there was no significantly increased hazard of parkinsonism among patients with cumulative gadolinium exposure compared with those exposed to non-gadolinium-enhanced MRIs (HR, 1.04 [95% CI, 0.98-1.09], *P* = .18, **Table 2**). No significantly increased HR was found in either sensitivity analysis.

**Discussion** | In this population-based study, no significant association between gadolinium exposure and parkinsonism was found. This result does not support the hypothesis that gadolinium deposits in the globus pallidi lead to neuronal damage manifesting as parkinsonism. However, reports of other nonspecific symptoms (pain, cognitive changes) after gadolinium exposure require further study.[1]

Strengths of the study include a large cohort with a similar propensity to use MRIs, assessment of more than 100 baseline characteristics, and methodology accounting for the cumulative nature of gadolinium exposure. A study limitation is the potential for differential misclassification of the outcome. Given the components of the outcome definition, it seems likely to be more sensitive and less specific among those with gadolinium exposure, which would mean the actual HR

may be lower than 1.04. Other limitations include the small number of patients who received 4 or more doses of gadolinium, the lack of generalizability to younger patients, the possibility of residual confounding from temporal trends in gadolinium usage not captured in the adjustment for year of initial MRI, and the inability to determine the specific type of gadolinium used.

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**1**. Ramalho J, Semelka RC, Ramalho M, Nunes RH, AlObaidy M, Castillo M. Gadolinium-based contrast agent accumulation and toxicity [published online December 10, 2015]. *AJNR Am J Neuroradiol*. doi:10.3174/ajnr.A4615.

**2**. Errante Y, Cirimele V, Mallio CA, Di Lazzaro V, Zobel BB, Quattrocchi CC. Progressive increase of T1 signal intensity of the dentate nucleus on unenhanced magnetic resonance images is associated with cumulative doses of intravenously administered gadodiamide in patients with normal renal function, suggesting dechelation. *Invest Radiol*. 2014;49(10):685-690.

**3**. Münchau A, Mathen D, Cox T, Quinn NP, Marsden CD, Bhatia KP. Unilateral lesions of the globus pallidus. *J Neurol Neurosurg Psychiatry*. 2000;69(4):494-498.

**4**. Butt DA, Tu K, Young J, et al. A validation study of administrative data algorithms to identify patients with parkinsonism with prevalence and incidence trends. *Neuroepidemiology*. 2014;43(1):28-37.

**5**. Welk B, McArthur E, Fraser L-A, et al. The risk of fall and fracture with the initiation of a prostate-selective α antagonist. *BMJ*. 2015;351:h5398.

**6**. Andersen PK, Gill RD. Cox's regression model for counting processes. *Ann Stat*. 1982;10(4):1100-1120. doi:10.1214/aos/1176345976.

## COMMENT & RESPONSE

### Human Granulocytic Anaplasmosis and Lyme Disease

**To the Editor** Human granulocytic anaplasmosis (HGA), caused by the rickettsia *Anaplasma phagocytophilum*, is vectored by the same *Ixodes* spp ticks that transmit Lyme disease. HGA is associated with fever, headache, cytopenia, and rarely mortality (if the infection occurs in elderly or immunocompromised hosts). HGA is not spread person-to-person by mucocutaneous exposure to the blood of infected patients; does not typically, or perhaps ever, cause bleeding from multiple body sites; is not usually associated with diarrhea; and has never been associated with relative bradycardia. Convalescent phase antibody titers to the etiologic agent reach 640 or greater in more than 90% of culture-confirmed cases in the United States, and morulae are detected on blood smears in more than 70% of such cases.[1]

In 2008, a report from China surprisingly claimed that a previously well 50-year-old woman, while hospitalized for what appeared to be a fatal viral hemorrhagic fever, infected 9 family members or health care workers with HGA.[2] However, the frequency and severity of the cytopenia in these 9 cases exceeded that expected for HGA,[1] most had diarrhea (n = 7), few had headache (n = 2), all had relative bradycardia, none had a convalescent HGA antibody titer that exceeded 256 (titers of 64-512 have been found in up to 20% of healthy people in China[3]), and none was morula positive. In addition, sequencing of the *groEL* gene product amplified by a nested polymerase chain reaction (PCR) assay was more similar to US strains than Chinese strains of *A phagocytophilum,* potentially consistent with the occurrence of laboratory contamination.[2]

This case cluster became more understandable with the discovery in China in 2011 of a novel bunyavirus, the severe fever with thrombocytopenia syndrome virus (SFTSV),[4] that causes an illness indistinguishable from that seen in the patients reported in 2008, including severe cytopenia, gastrointestinal manifestations, and relative bradycardia. A subsequent investigation of the index patient and all 9 of the secondary cases, conducted in part by 5 of the authors of the original report, demonstrated that all 10 patients were infected with SFTSV.[4] SFTSV is transmitted by ticks but not by *Ixodes* spp ticks. In addition, person-to-person transmission of SFTSV has been observed repeatedly.[4]

To establish the very unlikely possibility that all 10 patients in the original article were co-infected with both *A phagocytophilum* and SFTSV, the authors should have the